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EXAMINER	
CHONG, KIMBERLY	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/576,752	MCSWIGGEN ET AL.	
	Examiner	Art Unit	
	Kimberly Chong	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,13-21,30,31,36 and 37* is/are pending in the application.

4a) Of the above claim(s) *37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,13-21,30,31 and 36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 April 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant has canceled instant claim 33 thereby making the restriction requirement filed 03/21/2007 moot. Applicant has submitted new claim 37 and therefore restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1, 3, 13-21, 30-31 and 36, drawn to a chemically modified double stranded nucleic acid molecule wherein the antisense strand is complementary to a GPRA RNA, classifiable in class 536, subclass 24.5.

II. Claim 37, drawn to a method of inhibiting the expression of human GPRA, comprising administering a chemically modified double stranded nucleic acid molecule wherein the antisense strand is complementary to a GPRA RNA, classifiable in class 435, subclass 6 and 375.

The inventions are distinct, each from the other because of the following reasons:

Inventions of group I and group II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case the process can be practiced using a material different product, such as a single stranded nucleic acid molecule. Furthermore restriction is proper because the subject matter is divergent and non-coextensive.

Because these inventions are independent or distinct for the reasons given above and the inventions require a different field of search (see MPEP § 808.02), restriction for examination purposes as indicated is proper.

Because these inventions are independent or distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder. All claims directed a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product claim will not be rejoined. See MPEP

§ 821.04(b). Additionally, in order to retain the right to rejoinder in accordance with the above policy, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder**. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

During a telephone conversation with Anita Terpstra on 07/13/2007 a provisional election was made with traverse to prosecute the invention of group I, claims 1, 3, 13-21, 30-31 and 36. Affirmation of this election must be made by applicant in replying to this Office action. Claim 37 is withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Status of the Application

With entry of the amendment filed on 04/23/2007, claims 1, 3, 13-21, 30-31 and 36 are pending in the application and currently under examination.

Priority

Applicant does not receive the benefit of the earlier filed applications because the prior applications do not provide adequate support for the claims of the instant application and thus applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120.

Applicant points to support in priority application 60/363,124 however application 60/363,124 does not provide support for a chemically modified double stranded nucleic acid molecule targeted to a human GPRA nucleotide sequence wherein about 50-100%

of nucleotide positions in one or both strands of said double stranded nucleic acid molecule are chemically modified. Applicant also point to support in priority application 10/923,182 for a chemically modified double stranded nucleic acid molecule targeted to a human GPRA nucleotide sequence wherein about 50-100% of nucleotide positions in one or both strands of said double stranded nucleic acid molecule are chemically modified. Application, 10/923,182 is not listed as a priority document in the first paragraph of the instant specification nor is it listed on the Bib data sheet and therefore the instant application cannot claim benefit of application 10/923,182. Moreover, the priority provisional application 60/440,129 filed on January 15, 2003 expires within one year.

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

Due to the voluminous number of applications to which priority is now claimed, applicants are requested to point out with particularity to where such support may be found.

Thus, the claims are accorded a priority date of 07/16/2004, the filing date of the instant application.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 3, 13-21, 30-31 and 36 are provisionally rejected under the judicially created doctrine of double patenting over claims 1-5, 13-21, 31 and 36 of copending Application No. 10/923,182. This is a provisional double patenting rejection since the conflicting claims have not yet been patented. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims and the claims of the patent are drawn to patently indistinguishable subject matter.

The instant claims are drawn to a chemically modified double stranded nucleic acid molecule comprising a sense strand and an antisense strand wherein the antisense strand is complementary to a human GPRA nucleotide sequence (Genbank NM_207173), wherein each strand is 18 to 27 nucleotides in length, wherein about 50 to 100% of the nucleotides in each of the sense and antisense strands of the chemically modified double stranded nucleic acid molecule are modified with modifications selected

from 2'-O-methyl, 2'-O-fluoro, 2'-deoxy, phosphorothioate and deoxyabasic modifications and wherein one or more purine are 2'-O-methyl and one or more pyrimidines are 2'-fluro modifications, wherein the chemically modified double stranded nucleic acid molecule comprises one or more ribonucleotides, wherein one or more pyrimidine nucleotides in the sense strand are 2'-O-methyl or 2'-O-deoxy-2'-fluoro, wherein one or more purine nucleotides are 2'-deoxy or 2'-O-methyl, wherein the sense strand comprises a terminal cap moiety at the 5'-end, the 3'-end or both, wherein the antisense strand comprising a terminal phosphorothioate internucleotide linkage, wherein the 5' end includes a terminal 5'-phosphate and further drawn to a pharmaceutical composition comprising said chemically modified double stranded nucleic acid molecule.

Claims 1-5, 13-21, 31 and 36 of the copending Application No. 10/923,182 are drawn to a chemically modified double stranded nucleic acid molecule comprising a sense strand and an antisense strand wherein the antisense strand is complementary to a human GPRA nucleotide sequence (Genbank NM_207173), wherein each strand is 18 to 28 nucleotides in length, wherein about 100% of the nucleotides in each of the sense and antisense strands of the chemically modified, wherein the sense strand comprises a terminal cap moiety at the 5'-end, the 3'-end or both, wherein the antisense strand comprising a terminal phosphorothioate internucleotide linkage, wherein the 5' end includes a terminal 5'-phosphate and further drawn to a pharmaceutical composition comprising said chemically modified double stranded nucleic acid molecule. The specification of copending Application No. 10/923,182 discloses

modifications selected from 2'-O-methyl, 2'-O-fluoro, 2'-deoxy, phosphorothioate and deoxyabasic modifications and wherein one or more purine are 2'-O-methyl and one or more pyrimidines are 2'-fluro modifications, wherein the chemically modified double stranded nucleic acid molecule comprises one or more ribonucleotides, wherein one or more pyrimidine nucleotides in the sense strand are 2'-O-methyl or 2'-O-deoxy-2'-fluoro, wherein one or more purine nucleotides are 2'-deoxy or 2'-O-methyl.

Thus, claims 1-5, 13-21, 31 and 36 of the copending Application No. 10/923,182 anticipate the claims of the instant application. This is a provisional obviousness-type double patenting rejection.

New Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3, 13-17, 18-21, 30-31 and 36-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Laitinen et al. ("Laitinen I" WO 2004/056866), Laitinen et al. ("Laitinen II" Science 2004, Vol. 304: 300-304), Rana (US 2005/0020521), Matulic-Adamic (applicant's IDS) and evidenced by Caplen, N (applicant's IDS).

The instant claims are drawn to a chemically modified double stranded nucleic acid molecule comprising a sense strand and an antisense strand wherein the

antisense strand is complementary to a human GPRA nucleotide sequence, wherein each strand is 18 to 27 nucleotides in length, wherein about 50 to 100% of the nucleotides in each of the sense and antisense strands of the chemically modified double stranded nucleic acid molecule are modified with modifications selected from 2'-O-methyl, 2'-O-fluoro, 2'-deoxy, phosphorothioate and deoxyabasic modifications and wherein one or more purine are 2'-O-methyl and one or more pyrimidines are 2'-fluro modifications, wherein the chemically modified double stranded nucleic acid molecule comprises one or more ribonucleotides, wherein one or more pyrimidine nucleotides in the sense strand are 2'-O-methyl or 2'-O-deoxy-2'-fluoro, wherein one or more purine nucleotides are 2'-deoxy or 2'-O-methyl, wherein the sense strand comprises a terminal cap moiety at the 5'-end, the 3'-end or both, wherein the antisense strand comprising a terminal phosphorothioate internucleotide linkage, wherein the 5' end includes a terminal 5'-phosphate and further drawn to a pharmaceutical composition comprising said chemically modified double stranded nucleic acid molecule.

Laitinen I teach GPRA is involved in asthma (see page 40) and teach agents such as siRNA targeted to a gene encoding a human GPRA can be used to inhibit expression of GPRA (see page 41). Laitinen et al teach GPRA plays a strong role in the pathogenesis of asthma (see page 57). Laitinen II teach GPRA and it's downstream signaling pathways define a new pathway that is altered in asthma and teach GPRA is a strong candidate for a drug target involved in asthma as well as having a potential role in a wider spectrum of allergic disease that can be regulated by altering the expression

of GPRA (see pages 303-304). Laitinen I and Laitinen II do not teach chemical modifications of a siRNA.

Rana teach siRNA molecules which are 10-50 nucleotides in length and preferably 18-25 nucleotides in length that are capable of directing or mediating RNA interference (see paragraph 0070). Rana teach such siRNA molecules are comprised of separate sense and antisense strands wherein the siRNA comprises a sequence that is complementary to a target mRNA to direct target specific RNA interference. Rana further teach the siRNA comprises a 5' phosphate group attached to the hydroxyl group of the 5' sugar (see paragraph 0059). Rana teach that such siRNA can be modified at internal residues such that properties such as chemical stability and nuclease resistance are improved without compromising the RNA interference activity (see paragraph 0029). Rana teach that the RNAi mechanism does not require 2'-OH chemical groups and these groups could be replaced with such nucleotides such as 2'-deoxy, 2'-O methyl and 2'-fluoro and the siRNA was still able to efficiently induce RNAi in human cells. Rana teach the 3' terminal end or the 5' terminal end of the siRNA can be modified with such groups as peptides, cross linkers or organic compounds (see paragraph 0033). Rana teach pharmaceutical compositions comprising such siRNA (see paragraph 207). Rana teach the siRNA can comprise one or more chemical modifications in the sugar or nucleobase groups and teach the siRNA can comprise any combination of two or more modifications (see paragraphs 0036-0040). Rana teach that sense and/or antisense strands of such siRNA can comprise at least 100% of

chemically modified nucleotides and specifically teach such siRNA comprising 100% of chemically modified nucleotides are stable (see Figure 12).

Matulic-Adamic et al. teach double stranded structures comprising abasic terminal cap moieties that provide resistance to degradation (see column 2, lines 44-55 and column 3 lines 1-68).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make siRNA nucleic acid molecules targeted to GPRA, as taught by Latinen I, with chemical modifications in the sense or antisense strand, as taught by Rana and Matulic-Adamic et al.

One would have been motivated to incorporate modifications to the nucleotides of each strand of a siRNA to increase the siRNA nuclease resistance. Further, because Rana teach the RNAi mechanism does not require 2'-OH chemical groups, one of skill in the art would have been motivated to incorporate 2'-O-methyl, 2'-deoxy or 2'-deoxy-2'-fluoro chemical modifications in one or both strands as specifically taught by Rana to increase the duplex stability. Matulic-Adamic et al. provide motivation to make a siRNA with terminal cap moieties to provide resistance and degradation given that Matulic-Adamic et al. teach double stranded structures comprising terminal cap moieties. One would therefore be motivated to chemically enhance the siRNAs resistance to nucleases while preserving or maximizing its activity in order to most effectively target the desired gene. The motivation to chemically modify siRNA is further evidenced by Caplen (Expert Opin Biol Ther, 2003 Jul, 3(4), pp. 575-86), who points out that, "Many of the problems associated with developing RNAi as an effective therapeutic are the

same as encountered with previous gene therapy approaches. The key issues of delivering nucleic acids to the required tissue and cell type, while ensuring an appropriate level of efficacy with minimum toxicity induced by the vector system..." (see page 581). As evidenced by Caplen, RNA interference encounters similar problems as other nucleic acid based therapies and therefore, one would be motivated to incorporate each of the above-mentioned modifications in an attempt to enhance delivery of any of the sequence specific oligonucleotide therapeutics.

One would have had a reasonable expectation of success at introducing chemical modifications wherein about 100% of the nucleotides were modified given that Rana specifically teach such siRNA are more stable and such siRNA are capable of eliciting RNA interference activity in cells. Further, one would have a reasonable expectation of success because chemical modifications of an oligonucleotide, adding stability and specificity to oligonucleotides were known in the art at the time of the invention was made. Additionally, one would expect such modifications would benefit siRNAs because such modifications had been shown to benefit antisense or ribozymes.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention.

Claims 1, 3, 13-21, 30-31 and 36-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Laitinen et al. ("Laitinen I" WO 2004/056866), Laitinen et al. ("Laitinen II" Science 2004, Vol. 304: 300-304), Tuschl et al. (applicant's IDS), Parrish et al. (of record), Matulic-Adamic et al. (applicant's IDS) and Caplen, N. (applicant's IDS).

The instant claims are drawn to a chemically modified double stranded nucleic acid molecule comprising a sense strand and an antisense strand wherein the antisense strand is complementary to a human GPRA nucleotide sequence, wherein each strand is 18 to 27 nucleotides in length, wherein about 50 to 100% of the nucleotides in each of the sense and antisense strands of the chemically modified double stranded nucleic acid molecule are modified with modifications selected from 2'-O-methyl, 2'-O-fluoro, 2'-deoxy, phosphorothioate and deoxyabasic modifications and wherein one or more purine are 2'-O-methyl and one or more pyrimidines are 2'-fluro modifications, wherein the chemically modified double stranded nucleic acid molecule comprises one or more ribonucleotides, wherein one or more pyrimidine nucleotides in the sense strand are 2'-O-methyl or 2'-O-deoxy-2'-fluoro, wherein one or more purine nucleotides are 2'-deoxy or 2'-O-methyl, wherein the sense strand comprises a terminal cap moiety at the 5'-end, the 3'-end or both, wherein the terminal cap moiety is an inverted deoxy abasic moiety wherein the antisense strand comprising a terminal phosphorothioate internucleotide linkage, wherein the 5' end includes a terminal 5'-phosphate and further drawn to a pharmaceutical composition comprising said chemically modified double stranded nucleic acid molecule.

Laitinen I teach GPRA is involved in asthma (see page 40) and teach agents such as siRNA targeted to a gene encoding a human GPRA can be used to inhibit expression of GPRA (see page 41). Laitinen et al teach GPRA plays a strong role in the pathogenesis of asthma (see page 57). Laitinen II teach GPRA and it's downstream signaling pathways define a new pathway that is altered in asthma and teach GPRA is a

strong candidate for a drug target involved in asthma as well as having a potential role in a wider spectrum of allergic disease that can be regulated by altering the expression of GPRA (see pages 303-304). Laitinen I and Laitinen II do not teach chemical modifications of a siRNA.

Parrish et al. teach a double stranded nucleic acid with an antisense or sense region comprising 2'-deoxy-2'-fluoro pyrimidine nucleotides (see Figure 5) and further teach this double stranded nucleic acid can mediate degradation of cellular RNA (see abstract page 1082).

Tuschl et al. teach a siRNA, 19-25 nucleotides in length, wherein each separate strand comprises at least 19 nucleotides complementary to the nucleotides of the other strand (see Figure 14) and wherein the 5'-terminus of the antisense strand comprises a phosphate (see page 4, lines 12-20). Tuschl et al. teach the siRNA is least 85% complementary and more preferably 100% complementary to the target and that the siRNA are capable of mediating degradation of homologous RNAs. Tuschl et al. additionally teach siRNA molecules may contain at least one modified nucleotide analogue at either the 5' or 3' ends of the siRNA molecule (see page 5, lines 15-21). For example, the nucleotides may be modified at the 2' position of the ribose sugar. Preferred modifications are listed on page 6 and include 2'-O-alkyl and 2' fluoro modifications and Tuschl et al. specifically teach the preferred modifications may be combined in a single siRNA. Specific embodiments of modified siRNAs are taught at page 46 and Fig. 14, which describe and show results obtained with 2' modified siRNAs and teach siRNA comprising minimal modifications retain RNAi activity and further

teach modification of the entire double stranded RNA with 2'-O-methyl or 2'-deoxy is not well tolerated.

Tuschl et al. do not explicitly teach the optimum number and placement of 2'-sugar modifications such that siRNA activity is retained. However, Tuschl et al. clearly recognize and teach that 2'-modifications enhance the nuclease stability of siRNA molecules and that more extensive 2'-deoxy or 2'-O-methyl modifications reduce the ability of siRNAs to mediate RNAi. Thus, Tuschl et al. does recognize that chemical modification of the 2'-OH is an effective variable that may enhance nuclease resistance on the one hand and modulate siRNA activity on the other. Furthermore, Tuschl et al. suggests several types of substituents that may be used to replace the 2'-OH group, namely 2'-O-alkyl substituents (see page 6).

Matulic-Adamic et al. teach double stranded structures comprising abasic terminal cap moieties that provide resistance to degradation (see column 2, lines 44-55 and column 3 lines 1-68). Matulic-Adamic et al. further teach a double stranded structure comprising separate sense and antisense strands and further wherein this structure comprises a connecting loop comprising a linker or non-nucleotide linker (see Figure 3).

It would have been obvious to one of ordinary skill in the art at the time the invention was made and a matter of routine experimentation, to use the general conditions taught by Tuschl et al. for making 2'-modified siRNA to discover the optimal number and placement of 2'-sugar modifications in any siRNA molecule, such that the resulting siRNA molecule was endowed with maximum stability and functionality.

Additionally, it would have been obvious to one of ordinary skill in the art to incorporate known modifications, such as 2'-O-methyl, to impart increased stability and functionality in any siRNA because it is well known to one of skill in the art that modifications of RNA with 2'-O-methyl groups stabilize RNA and can protect RNA from nuclease degradation and one would be motivated to incorporate 2'-O-methyl groups to improve the efficacy of double stranded RNA. It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate terminal cap moieties and linker molecules as taught Matulic-Adamic and Thomson et al. into the siRNA as taught Tuschl et al. Further, it would have been obvious to incorporate 2'-fluoro modifications into said siRNA to enhance stability and nuclease resistance.

One would have been motivated to create such compounds with increased stability and functionality, and since siRNAs are taught by Tuschl et al. as being useful in cell culture and in whole organisms for elucidating gene function in culture and in whole organisms (paragraphs 29-30), which may be considered to be nuclease-rich environments. One would therefore be motivated to chemically enhance the siRNAs resistance to nucleases while preserving or maximizing its activity in order to most effectively target the desired gene. Further, Tuschl et al. teach 2'-O-methyl modification of both strands of the duplex as well as either sense or antisense strand alone, are not well tolerated (see Figure 14) and therefore one would have been motivated to search for particular chemical modifications that are tolerated by the double stranded RNA by routine experimentation of determining the optimum number and placement of the 2'-modifications to see how well the modifications were tolerated with respect to stability

and functionality of the dsRNA. Moreover, one would have been motivated to incorporate 2'-deoxy-2'fluoro modifications into said siRNA because Parrish et al. specifically teach 2'-deoxy-2'fluoro modifications incorporated into dsRNA are compatible with RNAi activity (see page 1081). Further, it would have been obvious to one or ordinary skill in the art to incorporate chemical modifications in all of the nucleotide positions on one or both strands of said double stranded RNA molecule as part of routine experimentation to further increase the efficacy of double stranded RNA molecules. Further, one would have been motivated to incorporate terminal cap moieties and linker molecules because Matulic-Adamic et al. teach terminal cap moieties provide nuclease resistance and protection from degradation and Thomson et al. teach connecting the sense and antisense strands via a linker increase efficiency of cleavage. Since each of the modifications were known to increase efficiency of oligonucleotide delivery and stability, one would have been motivated to incorporate into the siRNA molecules taught by Tuschl et al.

The motivation to chemically modify siRNA is further evidenced by Caplen (Expert Opin Biol Ther, 2003 Jul, 3(4), pp. 575-86), who points out that, "Many of the problems associated with developing RNAi as an effective therapeutic are the same as encountered with previous gene therapy approaches. The key issues of delivering nucleic acids to the required tissue and cell type, while ensuring an appropriate level of efficacy with minimum toxicity induced by the vector system..." (see page 581). As evidenced by Caplen, RNA interference encounters similar problems as other nucleic acid based therapies and therefore, one would be motivated to incorporate each of the

above-mentioned modifications in an attempt to enhance delivery of any of the sequence specific oligonucleotide therapeutics.

One would have a reasonable expectation of success given that Tuschl et al. teach how to make and use virtually any siRNA to any gene provided the target sequence is known and teach that methods of RNA synthesis are known in the art, as evidenced by the examples provided therein and further given that Parrish et al. teach sugar, base and phosphorothioate modifications are well tolerated in dsRNA involved in RNA interference. Further, one would have a reasonable expectation of success because chemical modifications of an oligonucleotide, adding stability and specificity to oligonucleotides were known in the art at the time of the invention was made. Additionally, one would expect such modifications would benefit siRNAs because such modifications had been shown to benefit antisense or ribozymes.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image

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KC
Examiner
Art Unit 1635

/Sean McGarry/
Primary Examiner
AU 1635